REMARKS

1. Per the Examiner's request for the Applicants to update the status of all US patent applications disclosed in the application, the Applicants amended the specification to update the status of the patent applications disclosed on page 4, lines 16-22, and on pages 13 to 14 of the instant application.

2. Regarding the Examiner's requirement to change the relationship of the application from a continuation to a continuation-in-part, the Applicants point out that the claims as amended herein are claims corresponding to the language in the specification as filed. Accordingly, this application is a continuation application of the prior filed application with no new matter.

Specifically, claims 1, 26, 33, and 38 have been amended to recite that the determinant is expressed on B cells of the individual and not expressed by immune cells other than B cells except for dendritic cells when the determinant is CD21. The amended recitation is supported in the specification at page 10, lines 17-22.

Claims 1, 26 and 33 have been amended to recite that treatment of the individual with the composition results in reduction of the pro-multiple sclerosis immune response. The amended recitation is supported in the specification at page 7, lines 12-19.

Claim 38 has been amended to delete lines 2 and 3 objected to by the Examiner, Claim 38 has also been amended to recite that the shed antigen comprises an epitope comprising a terminal 2,6 linked sialic acid. Support for this amendment is in the specification at page 13, lines 8-10.

Claim 45 has been amended to recite that the B cell determinant is on a B cell subpopulation altered in relative amounts in a human individual with a pro-multiple sclerosis immune response. Support for this amendment is in the specification in Example 1, particularly in Table 2, and page 20, lines 6-20.

Claim 48 has been amended to recite that the B cells have been activated by shed antigen, wherein shed antigen comprises terminal alpha 2, 6 linked sialic acid. Support for this amendment is in the specification on page 7, lines 1-7, and page 13, lines 8-10.

With respect to claims 22,23,30,31,37,43, and 44, and the Examiner's opinion that there is no support in the parent application for these claims, the Applicants respectfully disagree.

Claims 22, 30, 43 are clearly supported in the specification as filed (see, page 13, lines 8-10, and page 14, lines 1-2). Claims 23, 31, 37, 41, and 44 are clearly supported in the specification as filed (see, page 13, lines 8-10 and page 14, lines 1-5).

3. Rejection of claims 1, 18, 20-24, 26, 27, 29-34, 36-39, and 41-48 under 35 U.S.C. 112.

Reconsideration of the rejection of claims 1, 18, 20-24, 26, 27, 29-34, 36-39, and 41-48 under 35.U.S.C. 112 first paragraph is respectfully requested. Claims 1, 26, 33, 38, and 45 (and hence their respective dependent claims) have been amended to recite that the individual is a human individual; and thus, the antibody binds to the determinant of B cells on humans. The support in the specification for this amendment to claims 1, 26, 33, 38, and 45 may be found at page 14, lines 8-9.

It is noted for the record, that the amendments to the claims in points 2 & 3 above were in response to the objection of the claims under 35 U.S.C. section 112, and other claim objections by the Examiner. The Applicants have not amended the claims for purposes of narrowing their scope in view of any of the references cited by the Examiner as prior art. Therefore, under a *Festo* analysis, the claims should be entitled to the doctrine of equivalents within their full scope as filed in the instant application.

4. Regarding the application of references the Examiner has cited as prior art, this is a continuation application entitled to the priority of the parent application for the reasons stated above in item 2 herein.

5. Rejection of claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 under 35 U.S.C. 102. The U.S. Court of Appeals for the Federal Circuit court has repeatedly stated that anticipation under 35 U.S.C. 102 can only be established by a single prior art reference which discloses each and every element of the claimed invention. *RCA Corp. v. Applied Digital Data Systems, Inc.*, 730 F.2d 1440, 1444, 221 U.S.P.Q. (BNA) 385, 388 (Fed. Cir. 1984); *Radio Steel & Mfg. Co. v. MTD Products, Inc.*, 731 F.2d 840, 845, 221 U.S.P.Q. (BNA) 657, 661 (Fed. Cir. 1984); *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548, 220 U.S.P.Q. (BNA) 193, 198 (Fed. Cir. 1983); *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 772, 218 U.S.P.Q. (BNA) 781, 789 (Fed. Cir. 1983); *SSIH Equipment, S.A. v. U.S. Int'l. Trade Comm'n.*, 718 F.2d 365, 377, 218 U.S.P.Q. (BNA) 678, 688 (Fed. Cir. 1983). In other words, the cited reference must identically disclose and describe the claimed invention for the reference to anticipate the claimed invention under 35 U.S.C. 102.

Secondly, the Examiner is respectfully directed to MPEP 706.02(b) which states that a rejection based on 35 U.S.C. 102(b) can be overcome by establishing that the claims are patentably distinguishable over from the reference cited as prior art.

Third, the Examiner is respectfully directed to the Examiner's Office Actions mailed 07/06/2006 and 01/25/2007 for the instant application. In these Office Actions, the Examiner's position is that the claimed method involves B cell determinants which are chemically and functionally distinct, and therefore constitute patentably distinct species. Thus, the Applicants were required to elect a species of B cell determinant for searching with a method according to the present invention. The Applicants did not traverse the findings that the determinants were patentably distinct, but rather expressed that searching the generic class of the B cell determinants in B cell depletion would not be an undue burden on the Examiner. In the instant Office Action of the Examiner, item 1,

the Examiner again affirms that the aforementioned species are patentably distinct, and the requirement is therefore deemed proper and made FINAL. Further, it is acknowledged by the Examiner that the elected species is CD19.

A. In the instant Office Action, the Examiner rejects claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 under 35 U.S.C. 102(b) as being anticipated by Meyer et al. (EP 0332865). The Meyer et al. reference discloses a method to suppress the response of B lymphocytes in mammals to diagnostic or therapeutic doses of antibodies (see, for example, p. 2, lines 35-41); and this is done using selective suppression of B cells with a mature B lymphocyte surface marker (p. 3, lines15-17) using antibodies against Lym-1 (see Examples 1-9). The Examiner recognized that Meyer teaches only use of anti- B cell antibody recognizing the Lym-1 determinant.

For the reasons stated by the Examiner in the previous Office Actions for the instant application, which the Examiner held "final" in the instant Office Action, a method depleting B cells with a B cell determinant of Lym-1 is patentably distinct from a method of depleting B cells with a B cell determinant of CD19. CD19 is a determinant not limited to expression on mature B cells, as is the antibody to Lym-1 using in the method described by Meyer et al. Rather, CD19 is expressed on most B cells (immature and mature; See Appendix A hereto; "Principal Features of Known CD Molecules" from Cellular and Molecular Immunology). Thus, as the Examiner has stated in the previous Office Actions, the determinants are chemically and functionally distinct, and therefore patentably distinct.

A careful reading of Meyer et al. shows that they do not teach treatment of progressive MS with anti- B cell antibody Lym-1. What Meyer et al. teaches is that diagnostic antibodies or therapeutic antibodies used to treat humans can be recognized by the host's B lymphocytes which themselves may produce antibodies to neutralize the therapeutic antibody or diagnostic antibody (see p, 2, lines 7-20). Meyer et al. teach using the anti- B cell antibody Lym-1 in conjunction with therapeutic antibody or diagnostic antibody to suppress an immune response against the administered

therapeutic or diagnostic antibody (p.2, 38-40), not to treat a pro-MS immune response or MS itself. No disclosure of using the anti- B cell antibody Lym-1 to treat a pro-MS immune response and/or progressive MS is made, including in any form of administration (see claim 20, and species of site-directed). Rather, on page 3, lines 48-50, it is the therapeutic monoclonal antibody that is taught to be used in diseases such as progressive MS, not the anti- B cell antibody Lym-1.

In view that: (a) the Examiner has already held that the claimed method using an antibody against CD19 is patentably distinct from the method using an antibody against Lym-1, and that MPEP 706.02(b) states that a rejection based on 35 U.S.C. 102(b) can be overcome by establishing that the claims are patentably distinguishable over from the reference cited as prior art; and (b) Meyer et al. does not identically disclose or describe the claimed method; then claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 cannot be anticipated by Meyer et al. under the meaning of 25 U.S.C. 102(b). Accordingly, it is respectfully requested that this rejection be withdrawn.

B. In the instant Office Action, the Examiner rejects claims 45, 47 and 48 under 35 U.S.C. 102(b) or 102(e) as being anticipated by Arrufo et al. (U.S. Patent No. 6,051,228). The Examiner points out, in particular, column 21, lines 25-31. Line 25 reads as follows:

> "The antibodies of the present invention will typically find use in treating antibody mediated and/or T cell mediated disorders" (emphasis added).

It is known in the art that CD40 is not a B cell determinant, nor a determinant expressed on B cells but not on other immune cells. The Examiner is respectfully directed to Arrufo et al., column 1, lines 14-30. CD40 is expressed by B cells, dendritic cells, keratinocytes, monocytes, epithelial cells, endothelial cells, fibroblasts, eosinophils, and T cells (see also, Appendix A, macrophages). Thus, use of CD40 does not deplete B cells, but rather a whole host of immune cells, endothelial cells, epithelial cells, fibroblasts, etc. Since CD40 is functionally and chemically different than CD19, then a method of using an antibody against CD40 is patentably distinguishable from a method

of using an antibody against CD19. Further, Arrufo et al. fails to identically describe or disclose a method of depleting B cells to reduce a pro-multiple sclerosis immune response as recited in the amended claims of 45, 47 and 48.

In view that: (a) MPEP 706.02(b) states that a rejection based on 35 U.S.C. 102 can be overcome by establishing that the claims are patentably distinguishable over from the reference cited as prior art; and (b) Arrufo et al. does not identically disclose or describe the claimed method; then claims 45, 47 and 48 cannot be anticipated by Arrufo et al. under the meaning of 25 U.S.C. 102(b) or 102(e). Accordingly, it is respectfully requested that this rejection be withdrawn.

6. The Examiner's presumption, that the subject matter of the various claims was commonly owned at the time of the invention covered therein, is correct. The Applicants appreciate the Examiner's reminder.

7. Rejection of claims 1, 18, 20-24, 33, 34, 36-39 and 41-48 under 35 U.S.C. 103.

A. In the instant Office Action, the Examiner rejects claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 under 35 U.S.C. 103 as being unpatentable over Meyer et al. in view of Pesando (WO 91/13974) and Arrufo et al. The Examiner is respectfully reminded that "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". *In re Wesslau,* 353 F.2d at 241, 147 U.S.P.Q. at 393. In that regard, Meyer et al. do not teach treatment of progressive MS with anti- B cell antibody Lym-1. What Meyer et al. teaches is that diagnostic antibodies or therapeutic antibodies used to treat humans can be recognized by the host's B lymphocytes which themselves may produce antibodies to neutralize the therapeutic antibody or diagnostic antibody (see p, 2, lines 7-20). Meyer et al. teaches using the anti- B cell antibody Lym-1 in conjunction with therapeutic antibody or diagnostic antibody to suppress an immune response against the administered therapeutic or

diagnostic antibody (p.2, 38-40), not to treat a pro-MS immune response or MS itself. No disclosure of using the anti- B cell antibody Lym-1 to treat a pro-MS immune response and/or progressive MS is made. Rather, on page 3, lines 48-50, it is the therapeutic monoclonal antibody that is taught to be used in diseases such as progressive MS, not the anti- B cell antibody Lym-1. Arrufo et al. teaches using a pan-immune cell antibody recognizing the determinant CD40 (expressed by B cells, dendritic cells, keratinocytes, monocytes, macrophages, epithelial cells, endothelial cells, fibroblasts, eosinophils, and T cells). It is well known at the time of the invention that T cells and macrophages play a major role in causing multiple sclerosis (see, e.g., the instant application at p. 2 lines 10-21, and Table 1). Thus, use of an antibody against CD40 affects T cells and macrophages, and which constitutes a treatment totally different in function and therapeutic effect than depleting B cells associated with a pro-multiple sclerosis immune response. Pesando et al. teach a dual antibody approach, the combination of an antibody which binds to sIg on B cells and an antibody to CD19 in the form of a CD-19 specific immunoconjugate; and that only a subset of B cells possess sIg (see, for example, p. 4, lines 5-13). The combination of sIg and CD19 antibodies to form the immunoconjugate is directed to internalizing the immunoconjugate to the intracellular compartment of targeted B cells (see p. 3, lines 13-17).

The standard of patentability to be applied in obviousness rejections was enunciated by the Supreme Court in *Graham v. John Deere,* 383 U.S.1, 148 USPQ 459 (1966). In each and every case must be considered the scope and contents of the prior art, ascertaining the differences between the prior art and the claims in issue, resolving the level of ordinary skill in the pertinent art, and evaluating evidence of secondary considerations (see also MPEP 2100). The Supreme Court, in *KSR International Co., v. Teleflex Inc. et al.*, 127 S. Ct. 1727, at 1734 (also 82 U.S.P.Q.2D (BNA) 1385) reconfirms that these *Graham* factors are the framework to be applied for the statutory language of Section 103. In taking into consideration the *Graham* factors, the references individually and as a whole fail to teach, suggest or motivate one skilled in

the art at the time the invention was made to make the claimed method for the following reasons:

a) None of Meyer et al., Arrufo et al., or Pesando et al. individually, or combined, teach or suggest treatment of (i) a pro-multiple sclerosis immune response (which was unknown until disclosed by the instant application); (ii) reducing a pro-multiple sclerosis immune response by depleting B cells using an antibody targeting a determinant expressed by B cells and not by other immune cells (except for when the determinant is C21 wherein dendritic cells can also express the determinant) including in any form of administration (see claim 20, and species of site-directed); and (iii) reducing a pro-multiple sclerosis immune response by depleting B cells using an antibody targeting CD19 on B cells. The Examiner is reminded that the language in the claims "reducing a pro-multiple sclerosis" necessarily limits the claim, as it sets the framework of the invention which must be taken into consideration when determining if the scope and content of reference or a combination of references can be considered a prior art reference under section 103. See, e.g., *On Demand Machine Corporation v. Ingram Industries, Inc. et al.*, 442 F.3d 1331, 1343 (78 U.S.P.Q.2D (BNA) 1428) (Fed. Cir. 2006). To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of a claim against the prior art". *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494,496 (CCPA, 1970). See also, MPEP 2143.03. Due to the unobviousness of the elements of the claimed method according to the invention, the subject matter as a whole would not have been obvious to one of ordinary skill in the art at the time the invention was made.

b) A patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. Thus, the "subject matter as a whole" must be considered in determining obviousness of an invention under 35 U.S.C. section 103 (*In re Sponnoble*, 405 F.2d 578, 585, 160 U.S.P.Q. 237, 243 (CCPA, 1969). A pro-multiple sclerosis immune response caused by B cells, and induced by an antigen comprising an epitope comprising terminal alpha 2,6 linked sialic acid on shed antigen is the discovery of the source of a problem- exacerbation of multiple sclerosis. Thus, the scope and content of the references cited by the Examiner as a whole fail to teach or suggest a pro-multiple sclerosis immune response, or a method for reducing the pro-multiple sclerosis immune response by administering an antibody for depleting B cells (let alone an antibody directed against a determinant such as CD19) .

c) A prior art reference must be considered in its entirety, i.e., as a whole, including the portions that would lead or teach away from the claimed invention. *United States v. Adams* 383 U.S.39, at 51-52 (Supreme Court 1966); *W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 721 F. 2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983). See also MPEP 2145. Further, the references cannot be combined where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983). See also, MPEP 2145. Each of Meyer et al., Arrufo et al. and Pesando et al. teaches away from the claimed invention. Meyers et al. teaches using the anti- B cell antibody Lym-1 in conjunction with therapeutic antibody or diagnostic antibody to suppress an immune response against the administered therapeutic or diagnostic antibody, not to treat a pro-MS immune response or MS itself. Arrufo et al. teaches using a pan-immune cell antibody recognizing the determinant CD40, not a determinant expressed by B cells and not by other immune cells. Pesando et al. teach a dual antibody approach, the

combination of an antibody which binds to sIg on B cells and an antibody to CD19 in the form of a CD-19 specific immunoconjugate; and that only a subset of B cells possess sIg. These references, either singly or combined, teach away from using an antibody recognizing a determinant on B cells, such as CD19, to deplete B cells for reducing a pro-multiple sclerosis immune response. Instead they teach using combinations of antibodies, and/or antibody recognizing many different cell types other than B cells. Further, when combining the teachings and suggestions of Meyers et al., Arrufo et al. and Pesando et al., and taking their scope and content as a whole, one of ordinary skill in the art would still fail to come up with the claimed invention (let alone a reasonable expectation of success to make the claimed invention).

In view of the foregoing, the invention recited in claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 is patentable over the combination of Meyer et al. in view of Pesando (WO 91/13974) and Arrufo et al. within the meaning of under 35 U.S.C. 103. Accordingly, it is respectfully requested that this rejection be withdrawn.

B. In the instant Office Action, the Examiner rejects claims 20, 26, 27, and 29-32 under 35 U.S.C. 103 as being unpatentable over Meyer et al. in view of Pesando (WO 91/13974), Arrufo et al., and Turk et al. (U.S. Patent No. 5,958,409). Turk et al. disclose a method for treating multiple sclerosis using an anti-TNF-antibody. As explained in Turk et al. (column 3, lines 12 to 21), TNF is a secreted (not determinant found on) *in vivo* by monocytes and macrophages, and possibly some T cell subpopulations; and Turk et al. describe CNS-directed antibody administration using an anti-TNF-antibody. The combination of references fail to make the claimed invention obvious for the reasons stated (including case law citations, MPEP sections, and evidence of nonobviousness) as applied to the reconsideration of the rejection under section 103 of claims 1, 18, 20-24, 33, 34, 36-39, and 41-48 above. This can be summarized as follows.

a) None of Meyer et al., Arrufo et al., or Pesando et al., or Turk et al. individually, or combined, teach or suggest treatment of (i) a pro-multiple sclerosis immune response (which was unknown until disclosed by the instant application); (ii) reducing a pro-multiple sclerosis immune response by depleting B cells using an antibody targeting a determinant expressed by B cells and not by other immune cells (except for when the determinant is C21 wherein dendritic cells can also express the determinant); and (iii) reducing a pro-multiple sclerosis immune response by depleting B cells using an antibody targeting CD19 on B cells; regardless of the route of administration, such as but not limited to site-directed.

b) A patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. A pro-multiple sclerosis immune response caused by B cells, and induced by an antigen comprising an epitope comprising terminal alpha 2,6 linked sialic acid on shed antigen is the discovery of the source of a problem- exacerbation of multiple sclerosis. Thus, the scope and content of the references cited by the Examiner as a whole fail to teach or suggest a pro-multiple sclerosis immune response, or a method for reducing the pro-multiple sclerosis immune response by administering (regardless of the route of administration, such as but not limited to site-directed) an antibody for depleting B cells (let alone an antibody directed against a determinant such as CD19).

c) A prior art reference must be considered in its entirety, i.e., as a <u>whole</u>, including the portions that would lead or teach away from the claimed invention. Further, the references cannot be combined where the references teach away from their combination. Each of Meyer et al., Arrufo et al., Pesando et al., and Turk et al. teaches away from the claimed invention. Meyers et al. using the anti- B cell antibody Lym-1 in

conjunction with therapeutic antibody or diagnostic antibody to suppress an immune response against the administered therapeutic or diagnostic antibody, not to treat a pro-MS immune response or MS itself. Arrufo et al. teaches using a pan-immune cell antibody recognizing the determinant CD40, not a determinant expressed by B cells and not other immune cells. Pesando et al. teach a dual antibody approach, the combination of an antibody which binds to sIg on B cells and an antibody to CD19 in the form of a CD-19 specific immunoconjugate; and that only a subset of B cells possess sIg. Turk et al. teaches away from using an antibody recognizing (i) B cells, and (ii) a cell surface determinant (as Turk et al. teaches, TNF is a secreted molecule). These references, singly or combined, teach away from using an antibody recognizing a determinant on B cells, such as CD19, to deplete B cells for reducing a pro-multiple sclerosis immune response. Instead they teach using combinations of antibodies, and/or antibody recognizing many different cell types other than B cells, or soluble, secreted molecules rather than cell determinants. Further, when combining the teachings and suggestions of Meyers et al., Arrufo et al., Pesando et al., and Turk et al. and taking their scope and content as a whole, one of ordinary skill in the art would still fail to come up with the claimed invention (let alone a reasonable expectation of success to make the claimed invention).

In view of the foregoing, the invention recited in claims 20, 26, 27, and 29-32 is patentable over the combination of Meyer et al. in view of Pesando (WO 91/13974), Arrufo et al., and Turk et al. within the meaning of under 35 U.S.C. 103. Accordingly, it is respectfully requested that this rejection be withdrawn.

In view of the claim amendments, and the remarks including the citation of supporting case law and MPEP sections, Applicants believe the claims now meet the requirements of patentability under 35 USC §§ 112, 102, and 103 as cited by the Examiner. Examiner Schwadron, Ph.D. is respectfully encouraged to contact the undersigned

Applicants' representative if I can be of assistance to further the prosecution of this application; particularly if the Examiner feels an Examiner's Interview may be helpful to move this application towards allowance. The Applicants and the Applicants' representative understand and appreciate the U.S. Patent Office's goal to make the patent prosecution process more efficient, and we are willing to work with the Examiner to achieve the stated goal in this application.

Respectfully submitted,

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